Intravenous Enalapril Does Not Prevent Tachycardia-Induced Acute Atrial Electrical Remodeling

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Introduction and objectives. Recent clinical studies suggest a potential antiarrhythmic role of angiotensin-converting enzyme inhibitors in preventing atrial fibrillation. Studies in an animal model suggested that these drugs may prevent sustained atrial fibrillation by avoiding the occurrence of detrimental atrial electrical remodeling secondary to temporary episodes of fibrillation or atrial tachycardia. We sought to determine whether intravenous enalaprilat, administered at doses habitually used in clinical practice, prevented pacing-induced acute atrial remodeling.

Patients and method. We analyzed 16 patients with no structural heart disease referred for electrophysiologic study due to supraventricular tachycardia. During the control period, right and left atrial effective refractory periods (ERP) were determined before and after a 10-minute period of rapid atrial pacing (250 ms) to quantitatively assess pacing-induced shortening of the ERP. After full recovery, a bolus dose of enalaprilat (0.015 mg/kg) was infused and the measurement and stimulation procedure repeated to quantify remodeling after enalaprilat administration.

Results. In the control period, rapid pacing induced a significant 14% reduction (P < 0.01) in right atrial ERP and an 8% decrease (P < 0.01) in left atrial ERP as compared to baseline values. In the enalaprilat period, rapid pacing significantly reduced ERP by 15% in the right chamber (P < 0.01) and 7% in the left chamber (P < 0.01). There was no significant difference in the extent or time course of ERP shortening between the control and enalaprilat periods. The number of unintentionally induced atrial fibrillation episodes did not differ significantly between the two periods.

Conclusions. Intravenous enalapril does not avoid the occurrence of pacing-induced acute electrical atrial remodeling, modify its time course, or impede the induction of atrial fibrillation.

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El enalapril intravenoso no evita el desarrollo de remodelado eléctrico auricular agudo secundario a estimulación rápida

Introducción y objetivos. Estudios recientes sugieren un efecto antiarritmico de los inhibidores de la enzima de conversión de la angiotensina en la prevención de la fibrilación auricular. Un estudio realizado en animales sugirió que estos fármacos evitan el desarrollo del perjudicial remodelado eléctrico auricular agudo secundario a crisis de taquirrítmias auriculares. El presente estudio analiza en pacientes si el enalapril intravenoso en dosis convencionales previene el desarrollo de dicho remodelado.

Pacientes y método. Analizamos a 16 pacientes sin cardiopatía estructural remitidos para estudio electrofisiológico por taquirràcidas supraventriculares. En la fase control cuantificamos el remodelado eléctrico agudo mediante los períodos refratorios efectivos (PRE) en ambas aurículas antes y después de 10 min de estimulación auricular rápida (250 ms). Tras la recuperación de los PRE hasta valores basales, administramos enalaprilato intravenoso (0,015 mg/kg) y repetimos la secuencia previa de mediciones y estimulación para cuantificar el remodelado en fase enalapril.

Resultados. En fase de control, tras la estimulación rápida se indujo una significativa reducción del 14% en los PRE derechos (p < 0,01) y del 8% en los izquierdos (p < 0,01) respecto a sus valores basales. En la fase enalapril, los PRE descendieron un 15% (p < 0,01) y un 7% (p < 0,01), respectivamente. Comparando ambas fases, no hubo diferencias significativas en el grado de remodelado ni en su evolución temporal. El número de episodios de fibrilación auricular inducidos inintencionadamente durante las mediciones de los PRE no varió de manera significativa entre ambas fases.

Conclusiones. El enalapril intravenoso no evita el desarrollo de remodelado eléctrico auricular agudo, no modifica su duración ni dificulta la inducción de fibrilación auricular.

Palabras clave: Remodelado. Inhibidores de la enzima de conversión de la angiotensina. Fibrilación auricular.
PATIENTS AND METHODS

Population

The study was approved by the Ethics Committee of our center in accordance with the guidelines of the Declaration of Helsinki. We studied patients referred to our unit for electrophysiological examination and ablation of paroxysmal tachycardia with narrow QRS complex. Patients with echocardiography showing significant structural heart disease, including moderate or severe hypertrophy and anteroposterior left atrial diameter greater than 45 mm, incessant tachycardia or tachycardia lasting more than 30 min in the previous 10 days, and a history of atrial tachyarrhythmias were excluded. Patients with a history of treatment with ACE inhibitors, angiotensin II receptor antagonists or amiodarone were also excluded. Any other antiarrhythmic agent had to have been suspended for at least 5 half-lives. Likewise, patients with basal hypotension (systolic blood pressure <95 mm Hg or diastolic blood pressure <60 mm Hg), hyperpotassemia, risk of pregnancy, or clinical or analytical suspicion of renal dysfunction were excluded. Patients who had tachycardia for more than 10 successive minutes during the electrophysiological diagnosis did not undergo further study procedures.

Study Procedures

After the patients had signed a specific informed consent, examinations were performed with no sedatives and while fasting. Three catheter electrodes, 2 quadripolar with an interelectrode separation of 2-5-2 mm (Daig, St Jude Medical) and 1 decapolar (Daig, St Jude Medical) were introduced along the femoral vein. The 2 quadripolar electrodes were placed in the right appendage of the right atrial free wall and the decapolar catheter was introduced into the coronary sinus with its distal dipole in the lateral region of the mitral annulus. The right atrium was paced from the catheter in the free wall. The distal dipole of the catheters in the right appendage and the coronary sinus were used to measure the right and left AERP, respectively. The local bipolar electrograms (filtered at 30-500 Hz) and the surface electrocardiogram were recorded digitally with a polygraph (Cardiolab-II, Prucka Engineering, General Electric). A programmable electric pacer (UHS 20, Biotronik) was used. In the first 10 patients, right atrial pressure was monitored for 30 minutes after infusion of enaprilat with an angiographic catheter. Blood pressure was measured non-invasively.

Control Phase: Basal and Post-Pacing Measurements

The basal right and left AERP were measured at le-
ast 10 minutes after the last induced tachycardia at drive cycle lengths of 500, 400, and 300 ms with a drive train of 8 beats and pacing at twice diastolic threshold. Increments of 5 ms were used to avoid episodes of AF, which, particularly if prolonged, could alter the study procedure and the results. As in the study by Nakashima et al.9 we defined AERP as the shortest S1-S1 interval that induced propagation of an atrial response. Basal AERP were recorded in triplicate and the average was taken.

After measurement of basal AERP, the right atrium was paced at drive cycle lengths of 250 ms for 10 minutes at twice diastolic threshold. Immediately after pacing, the right AERP then left AERP were measured at drive cycle lengths of 500, 400 and 300 ms. To determine the changes in refractory periods, right and left AERP were measured every 3 minutes with drive cycle lengths of 500 ms until basal values were attained once again. After pacing, each AERP was measured at only one drive cycle length because acute remodeling is short-lived in similar models.7,8

Enalaprilat Phase: Basal and Post-Pacing Measurements

Fifteen minutes after complete recovery of AERP, we infused enalaprilat (0.015 mg/kg, up to a maximum of 1 mg) for 5 minutes. At least 20 minutes later—the exact delay depended on the ablation procedure—we repeated the control phase sequence. Thus, we measured right and left AERP at drive cycle lengths of 500, 400, and 300 ms, before (basal values in enalaprilat phase) and immediately after an additional cycle of 10 minutes of atrial pacing at 250 ms. The new AERP were measured after pacing, and right and left AERP were determined every 3 minutes at 500 ms and compared with the control phase. An irregular repetitive atrial response with a mean cycle time less than 300 ms that lasted more than 3 seconds was recorded as an episode of unintentionally induced AF.

Statistical Analysis

Values are expressed as mean ± standard deviation (SD). The Student t-test for unpaired data was used to compare parametric variables. Non-parametric data were compared using the Fisher exact test. Changes in hemodynamic variables were studied with the ANOVA test for repeated measurements with contrast analysis. Significance was set at a bilateral probability of $P<.05$. The computer program SPSS 9.0 was used.

RESULTS

We included 16 patients—6 of whom were male—with a mean age of 46.1±14 years (range, 20-78 years). The mean ejection fraction was 0.64±0.04. Two patients had been diagnosed as hypertensive prior to entry in the study, but were well controlled with thiazides and showed no significant hypertrophy in the echocardiogram. Atroventricular tachycardia was induced in 13 patients. The 3 remaining ones had accessory pathway mediated tachycardia. No significant complications were reported after any ablations. Two patients required isoproterenol at low doses (1 µg/kg/min) to induce clinical tachycardia. The study procedure began immediately after tachycardia had ceased completely and basal heart rate had been reached.

Acute Electrical Remodeling in Control Phase

The basal right AERPs in the control phase were 201.5±25.3 ms at 500 ms drive cycle, 194.6±23.9 ms at 400 ms drive cycle, and 177.0±17.2 ms at 300 ms drive cycle (Table 1). Basal left AERPs in the coronary sinus were 237.6±16.3 ms (500 ms drive cycle), 224.7±14.3 ms (400 ms drive cycle), and 193.1±12.2 ms (300 ms drive cycle). After rapid atrial pacing, right AERPs decreased significantly to 173.1±25.4 ms (mean percentage change of −14±14.6%; $P<.01$) at 500 ms drive cycle, 172.8±22.3 ms (−11.±7.4%; $P<.01$) at 400 ms drive cycle, and 162.8±16.6 ms (−8.0±6.7%; $P<.02$) at 300 ms drive cycle. After measurement of the right AERPs, the left AERP were measured (73±14 seconds after the end of rapid atrial pacing). These also decreased significantly at the 3 drive cycle lengths to 219.7±11.6 ms (−7.6±6.2%; $P<.01$) at 500 ms drive cycle, 210.3±11.7 ms (−6.9±5.0%; $P<.01$) at 400 ms drive cycle, and 183.0±11.1 ms (−5.0±4.1%; $P<.02$) at 300 ms drive cycle. The left

| TABLE 1. Right and Left Atrial Effective Refractory Periods Measured at 3 Drive Cycle Lengths (DCL) Before and After Rapid Atrial Pacing (RAP): Values for Control Phase and Enalaprilat Phase (EN) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Control         | EN              | Control         | EN              |
|                | Pre-RAP         | Post-RAP        | Pre-RAP         | Post-RAP        |
| RA              |                 |                 |                 |                 |
| DCL 500        | 201.5±25.3      | 173.1±25.4      | 200.0±27.2      | 169.7±19.5      |
| DCL 400        | 194.6±23.9      | 172.8±22.3      | 191.3±22.6      | 171.6±19.7      |
| DCL 300        | 177.0±17.2      | 162.8±16.6      | 177.4±16.4      | 163.7±17.2      |
| LA              |                 |                 |                 |                 |
| DCL 500        | 237.6±16.3      | 219.7±11.6      | 234.2±14.1      | 217.8±5.6       |
| DCL 400        | 224.7±14.3      | 210.3±11.7      | 221.1±8.8       | 204.5±14.8      |
| DCL 300        | 193.1±12.2      | 183.0±11.1      | 189.0±11.3      | 183.1±13.1      |

Data expressed as mean ± SD in milliseconds. Total number of patients studied in both phases: 16.

* $P<.01$, † $P<.02$, ‡ $P<.11$ compared with pre-RAP values from the same group.

§ $P$ not significant, compared with pre-RAP value in control phase. †† $P$ not significant, compared with post-RAP value in control phase.
AERP at 300 ms was measured 114±15 seconds after pacing had finished.

Complete recovery from shortening of AERP occurred after 8.4±3.2 minutes for the right atrium and 7.5±3.1 minutes for the left (Figure 1).

Before rapid atrial pacing, self-limiting episodes of AF were induced during 2.8% of the measurements of basal right AERPs (Table 2). After pacing, the number of episodes of AF induced increased significantly to 8.9%. No episodes were induced during measurement of basal left AERPs, whereas 1.6% of measurements after rapid atrial pacing induced episodes of AF.

### Acute Electrical Remodeling in Enalaprilat Phase

At 39±34 minutes (range, 21-113 minutes) after the start of enalaprilat infusion, the basal right and left AERPs were measured once again. The new right basal AERPs were 200.0±27.2 ms at 500 ms drive cycle, 191.3±22.6 ms at 400 ms drive cycle, and 177.4±16.4 ms at 300 ms drive cycle. The basal AERPs in the enalaprilat phase were 234.2±14.1 ms at 500 ms drive cycle, 221.1±8.8 ms at 400 ms drive cycle, and 189.0±11.3 ms at 300 ms drive cycle. These values did not differ significantly from the basal values of the control phase in either atrium (Table 1).

Immediately after an additional 10-minute cycle of rapid atrial pacing at 250 ms, the right AERPs decreased significantly to 169.7±19.5 ms at 500 ms drive cycle (mean percentage decrease of −15.1±9.6%; P<.01), 171.6±19.7 ms at 400 ms drive cycle (−10.3±4.3%; P<.01), and 163.7±17.2 ms at 300 ms drive cycle (−7.7±4.5%; P<.01) (Table 1). After measurement of the right AERPs, the new left AERPs were determined at a mean of 71±14 seconds after atrial pacing. The left AERPs after pacing were significantly less at 500 and 400 ms: 217.8±15.6 ms (change of −7.0±6.1%; P<.01) and 204.5±14.8 ms (−7.5±6.7%; P<.01), respectively. The new left AERP at 300 ms drive cycle decreased to 183.1±13.1 ms (−3.2±4.5%; P=.11; Table 1), though the difference was not significant. The last AERP was measured after right AERPs, a fact which might explain their post-pacing shortening. RAc indicates right atrium in control phase; RAe, right atrium in enalaprilat phase; LAc, left atrium in control phase; LAe, left atrium in EN phase.

**TABLE 2.** Atrial Fibrillation Episodes Unintentionally Induced While Measuring the Atrial Effective Refractory Periods

<table>
<thead>
<tr>
<th>Episodes/Measurements</th>
<th>Patients</th>
<th>Episodes/Measurements</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA 4/144 (2.8%)</td>
<td>3</td>
<td>11/123 (8.9%)</td>
<td>5</td>
</tr>
<tr>
<td>LA 0/144 (0%)</td>
<td>0</td>
<td>2/123 (1.6%)</td>
<td>1</td>
</tr>
<tr>
<td>EN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA 5/144 (3.5%)</td>
<td>2</td>
<td>8/128 (6.5%)</td>
<td>4</td>
</tr>
<tr>
<td>LA 0/144 (0%)</td>
<td>0</td>
<td>0/128 (0%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*RA indicates right atrium; LA, left atrium.
Total number of patients studied in both phases: 16.
1P<.04 compared with the pre-RAP value for RA in control phase. 2P not significant, compared to the pre-RAP value for RA in EN phase. 3P not significant, compared to post-RAP value for RA in control phase.
In the enalaprilat phase, 3.5% of the measurements of basal right AERPs induced brief episodes of AF, whereas AF was induced during 6.5% of the measurements after pacing, but this difference was not statistically significant. After pacing, fewer episodes of AF were induced in the enalaprilat phase during measurement of right AERPs than in the control phase, but the difference was not significant (6.5% vs 8.9%, respectively). In the enalaprilat phase, measurement of left AERPs did not induce any episodes of AF before or after pacing (Table 2). No significant differences were found in the mean duration of induced episodes of FA between the control phase and the enalaprilat phase after pacing (4.9±3.4 seconds for control phase vs 5.1±3.8 seconds for enalaprilat phase).

**Hemodynamic Parameters**

Enalaprilat was well tolerated clinically and no significant episode of hypotension was reported (defined as ≤90/60 mm Hg) during 6-hour follow up. Mean blood pressure decreased significantly from 105.9±9.5 mm Hg after 30 minutes to 89.7±6.7 mm Hg after 60 minutes (P<0.03; Table 3). No significant differences were found in heart rate during the study. Right atrial pressure did not change significantly during the 30-minute recording period (Table 3).

**DISCUSSION**

**Main Findings**

This study investigated for the first time whether acute administration of an ACE inhibitor affects acute electric remodeling in human atria. Rapid atrial pacing for 10 minutes reduced AERPs in both atria. The effect was more marked in the right atrium, probably because the measurements on the left atrium were performed 1 minute later, thus allowing more time for recovery from remodeling. The size of the decrease in the right AERPs was comparable to that induced by a 10-minute episode of AF. Intravenous enalaprilat did not prevent the appearance of remodeling or alter its duration or progression over time (Figure 1).

**Inhibition of Angiotensin II and Prevention of Atrial Electrical Remodeling**

The proarrhythmic effects of angiotensin II have been characterized, and there is evidence of a potential benefit of inhibition. Stretching of heart tissue increases synthesis of angiotensin II, favoring hypertrophy and, thus, a proarrhythmic substrate. Angiotensin II favors dispersion of the repolarization by modulation of ion channels. It has therefore been shown that administration of angiotensin II increases right atrial pressure, which could favor onset of AF.

Decreases in concentrations of angiotensin II after administration of oral ACE inhibitors have been shown to lower the incidence of AF in clinical studies of heart failure. Sustained use of the angiotensin receptor antagonist irbesartan increases the time to first recurrence in patients with cardioversion. Likewise, animal models of heart failure show that sustained treatment with oral ACE inhibitors decreases the extent of atrial fibrosis, improves atrial contractile function, prevents deterioration in atrial conduction and is associated with a shorter duration of the AF episodes induced. This suggests that such drugs may be useful in the prevention of chronic atrial structural remodeling secondary to heart disease, whereas a canine model with atrial pacing for 7 days showed that treatment with oral enalapril did not prevent chronic atrial electrical remodeling.

With regard to acute electric remodeling, Nakashima et al showed that intravenous administration of captopril or candesartan completely prevented the appearance of acute electric remodeling after rapid atrial pacing in a small canine series, contrary to our results. In the same study, acute administration of angiotensin II increased such remodeling. Our study procedures differ on several points from this study in dogs. In the animal model, infusion started 30 minutes before rapid pacing and continued during the 3 hours of pacing. Despite the long period of pacing, the extent of remodeling in the control group, measured as a drop in AERP, was quantitatively similar to our series. Our study used enalaprilat at normal clinical doses for hypertension. In the animal model, the total dose of captopril administered was 10 times greater than the
Direct Antiarrhythmic Effect on Ion Channels

In addition to lowering the concentrations of angiotensin II, acute administration of enalaprilat might affect electrical atrial remodeling by directly modifying ion channels. The angiotensin II receptor antagonists candesartan and losartan have been shown to block potassium channels, thus prolonging the action potential. These antagonists could therefore have an antiarrhythmic effect regardless of their effect on angiotensin II, but the only similar study with an ACE inhibitor, in this case lisinopril, did not show a direct antiarrhythmic effect on the main atrial ion channels.

Other Mechanisms Implicated in Acute Atrial Electrical Remodeling

Our results suggest that angiotensin II does not significantly mediate acute atrial electrical remodeling. Many studies have shown that other mechanisms may be implicated. A key factor seems to be overload of intracellular calcium, secondary to persistent tachycardia. In fact, calcium channel blockers have been shown to slow the development of acute remodeling. Recently, new mechanisms have been discussed, such as the sodium-proton exchanger, and 4-aminopiridine sensitive potassium channels and 17 betaestradiol. Finally, of the conventional antiarrhythmic drugs other than calcium channel blockers, only ibutilide has been shown to decrease acute atrial electrical remodeling.

Limitations

To prevent potential confounding factors, we selected patients with no significant heart disease or history of AF. Our findings cannot therefore be directly extrapolated to other types of patient. The time between infusion of enalaprilat and assessment of remodeling was not the same for all patients. Ten patients were analyzed 24±2 minutes after the start of infusion. This period might be too short, thus underestimating the real effect of enalaprilat. However, the decrease in plasma concentrations of angiotensin II after administration of intravenous enalaprilat is almost instantaneous. The onset of the hypotensive effect of intravenous enalaprilat occurs at less than 5 minutes, and the peak effect is observed between 30 minutes and 4 hours after start of administration. Moreover, 6 patients were studied more than 1 hour after the start of administration of enalaprilat, with similar results.

Enalaprilat significantly lowered blood pressure. The sympathetic activation could affect AERPs and mask the real effect of enalaprilat in remodeling, though the absence of significant changes in heart rate and the lack of change from baseline of AERPs after drug administration suggest that such activation is small. We did not induce pharmacological blockade of the autonomic nervous system for measurement of AERP because we thought the changes recorded would have been minimal. Moreover, autonomic blockade would have little clinical effect if all changes were positive.

The dispersion in our measurements was such that 33 patients would be necessary to reach a power of 80% in a study of equivalence. The difference for which a result could be considered equivalent would be 15 ms, with a power of 80% and an alpha error of 0.05, for a mean difference between the control phase and the enalaprilat phase of 20 ms and an SD of 20 ms. Given that enalaprilat does not show any favorable tendency after evaluation of 16 patients in an invasive study, we think that it is reasonable to assume that enalaprilat does not prevent acute electrical remodeling.

TABLE 3. Hemodynamic Data in EN Phase: Before and After Drug Administration*

<table>
<thead>
<tr>
<th></th>
<th>Pre-EN</th>
<th>5 Minutes</th>
<th>30 Minutes</th>
<th>60 Minutes</th>
<th>120 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>84.4±9.2</td>
<td>85.6±11.3</td>
<td>82.5±9.1</td>
<td>81.2±12.5</td>
<td>82.2±14.5</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>100.4±11.3</td>
<td>103.8±14.4</td>
<td>105.9±9.5</td>
<td>89.7±6.7(†)</td>
<td>89.3±15.9</td>
</tr>
<tr>
<td>RABP, mm Hg</td>
<td>6.1±2.8</td>
<td>5.8±2.7</td>
<td>6.2±3.7</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Data expressed as mean ± standard deviation. N=16 for HR and MBP; N=10 for RABP.

*Pre-EN indicates values immediately prior to drug infusion; EN, enalaprilat; HR, heart rate; MBP, mean blood pressure; RABP, mean right atrial pressure.

\(†\)P<.03 with respect to prior measurement of MBP.
Intravenous enalaprilat does not seem to prevent shortening of AERP secondary to rapid atrial pacing in patients with no structural heart disease or history atrial arrhythmias. Our results suggest that angiotensin II does not significantly participate in acute atrial electrical remodeling in normal conditions. Further studies will be necessary to determine whether enalaprilat can alter remodeling in patients with structural heart disease, who would probably have higher concentrations of angiotensin II, or in patients with a history of AF.

**REFERENCES**